IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF OHIO
WESTERN DIVISION

Anthony DeGidio,

Plaintiff

v.

Centocor Ortho Biotech, Inc., et al.,

Defendants

Case No. 3:09CV721

ORDER

In this pharmaceutical products-liability suit governed by Ohio law, plaintiff Anthony DeGidio alleges that defendant Centocor Ortho Biotech, Inc.[1], the developer and manufacturer of the immunosuppressant drug Remicade, failed to warn that taking Remicade can cause non-infectious interstitial lung disease. Plaintiff alleges he contracted this condition, which severely impairs his ability to breathe, after taking Remicade to treat his Crohn's disease.

Jurisdiction is proper under 28 U.S.C. § 1332(a)(1).

Now pending are Centocor's motions under *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579 (1993), to exclude plaintiff's three expert witnesses, each of whom intends to opine that Remicade can and did cause plaintiff's lung injury. (Docs. 115, 116). Centocor also filed a partial motion for summary judgment, contending that, if I grant the *Daubert* motions, plaintiff would have no admissible evidence to prove proximate cause. (Doc. 124).

[1] There are multiple defendants, but I need not discuss them separately.

For the reasons that follow, I grant the motions to exclude plaintiff's experts and, of necessity, grant Centocor's motion for summary judgment.

Background

Plaintiff is a fifty-nine-year-old man who has suffered from Crohn's disease since the 1970s. In 2008, plaintiff's treating physician, Dr. Gregory Slee, opined that plaintiff's Crohn's disease was so severe that, absent a liver transplant, plaintiff's life expectancy was less than ten years. Plaintiff represents that, due to the injuries at issue in this case, he is no longer a viable candidate for transplant surgery.

Crohn's disease is a chronic, incurable inflammatory disease affecting the gastrointestinal tract. In Crohn's disease, the body's blood cells produce a substance called tumor necrosis factor alpha (TNF-α), which causes the immune system to attack healthy tissues.

Remicade is a prescription drug approved by the FDA to treat moderate and severe manifestations of Crohn's disease. Remicade, also known by the generic name infliximab, is a biologic chimeric monoclonal antibody directed at TNF-α. It works by attaching to TNF-α molecules and blocking their attacks on the body's healthy tissues – in effect, suppressing the body's immune system. Because of its ability to block TNF-α molecules, medical professionals sometimes refer to Remicade as a TNF-α inhibitor or an anti-TNF-α agent.

There is widespread agreement in the medical community that Remicade, which is administered via intravenous infusions, is effective at reducing inflammation and alleviating pain associated with Crohn's disease.

A. The Remicade Infusions

Between 1974 and 2010, plaintiff underwent three Crohn's-related surgeries and was hospitalized roughly thirty times for severe abdominal pain and bowel obstructions.

In April, 2005, plaintiff's condition worsened dramatically: he experienced great pain, was hospitalized, and needed a blood transfusion. Dr. Slee determined to treat plaintiff with Remicade. Plaintiff received his first infusion of Remicade on April 25, 2007; he received additional infusions on May 14, June 12, and August 8.

While he was receiving Remicade, plaintiff also took Pentasa (generic name mesalamine), a prescription drug used to treat ulcerative colitis. Plaintiff's medical records reflect that he took Pentasa on a daily basis from April 23, 2007, to September 28, 2007. Medical professionals agree that Pentasa is associated with interstitial lung disease.

After his second infusion of Remicade, plaintiff developed a cough and reported feeling fatigued during the previous two weeks; he later reported a burning sensation in his chest. On September 19, 2007, after plaintiff was diagnosed with bilateral pneumonia, he was admitted to Toledo Hospital.

However, plaintiff's condition only deteriorated, and his doctors transferred him, via airlift, to the University of Michigan Hospital (UMH) in late September. Plaintiff remained at UMH for several weeks, receiving treatment for pulmonary injuries and other conditions related to Crohn's and liver disease. On his admission to UMH, however, plaintiff stopped taking Pentasa.

Doctors at UMH reviewed plaintiff's lung biopsy and determined that he was suffering from "Remicade-induced eosinophilic pneumonitis with no clear infectious etiology." *DeGidio v. Centocor Ortho Biotech*, 2010 WL 4628903, at *1 (N.D. Ohio 2010).

Plaintiff was finally discharged from UMH in December, 2007.

The parties in this case have retained numerous experts to opine on the nature and etiology of plaintiff's lung disease. Although their opinions conflict on many points, the experts generally agree that plaintiff's condition can be described as interstitial pneumonitis. An interstitial lung disease in one that affects the interstitium, the tissue and space around the lung's air sacs. The "pneumonitis" component refers to an inflammation generally associated with a non-infectious cause (in contrast with pneumonia, which generally – though not always – indicates an infectious cause and the collection of fluid in the lung tissue).

The experts further agree that the type of damage observed in plaintiff's lung tissue is best described as diffuse alveolar damage. This damage, which is permanent in nature, is characterized by the replacement of healthy lung tissue with excessively fibrous tissue. As one of plaintiff's experts explained, the fibrosis in plaintiff's lungs "is the result of the interstitial pneumonitis. It's the chronic phase." (Doc. 113-1 at 91).

B. Prior Proceedings

In a prior order, I denied Centocor's first motion for summary judgment. Centocor had argued that, because Remicade's package insert warned that taking Remicade could cause pneumonia, there was no genuine dispute as to the adequacy of the warnings. However, I concluded that the label warned of the risk of only infectious-based pneumonia, and that plaintiff had shown a genuine dispute "on the narrow issue of whether the label on its face warned of Remicade-induced [interstitial lung disease]." *DeGidio*, *supra*, 2010 WL 4628903, at *5.

C. Proposed Expert Testimony

To prevail on his failure-to-warn claim, plaintiff must establish that the allegedly inadequate warnings on the Remicade package insert proximately caused his injury. *Graham v. Am. Cyanamid Co.*, 350 F.3d 496, 514 (6th Cir. 2003).

The proximate-cause element has two components: general causation and specific causation. *In re Meridia Prods. Liab. Litig.*, 328 F. Supp. 2d 791, 798 (N.D. Ohio 2004), *aff'd*, 447 F.3d 861 (6th Cir. 2006). General causation "addresses whether a substance is capable of causing a particular injury or condition in the general population." *Terry v. Caputo*, 115 Ohio St. 3d 351, 355 (2007). Specific causation "relates to whether a substance caused a particular individual's injury." *Id.*

Plaintiff proposes to call three expert witnesses to opine on general and specific causation.

1. Dr. Thornton

Dr. Mark Thornton is a consultant at the pharmaceutical-consulting company, xFDA. He holds a Master's of Public Health and a Ph.D. in Pharmacology and Toxicology. From 1995 to 1997, and 1999 to 2001, Thornton worked as a Medical Officer at the FDA's Center for Biologic Evaluation and Research. At the FDA, Dr. Thornton led the clinical review team that approved the use of Remicade to treat Crohn's disease.

Dr. Thornton opined that "one can conclude that Mr. DeGidio's injuries . . . were proximately caused by his use of infliximab." (Doc. 115-2 at 5-6).

Implicit in that opinion was Thornton's conclusion that Remicade can cause interstitial pneumonitis. The doctor based that part of his opinion on case reports appearing in medical journals, which describe "clinical events in one or more individuals. They report unusual or new disease presentations, treatments, manifestations, or suspected associations between two diseases, effects

of medication, or external causes." *Caraker v. Sandoz Pharm. Corp.*, 188 F. Supp. 2d 1026, 1034 (S.D. Ill. 2001).

Thornton explained that, as early as 2001, "case reports began . . . noting the onset of non-infectious pulmonary complications of TNF inhibitor therapy, including eosinophilic pneumonitis, pulmonary fibrosis/interstitial lung disease, granulomatous disease and alveolar hemorrhage." (Doc. 115-2 at 2).

Among the reports that Thornton cited was Dotan, et al., *Treatment of Crohn's disease with anti TNF alpha antibodies–the experience in the Tel Aviv Medical Center* (2001). According to the report's abstract,[2] doctors at the Tel Aviv Medical Center who treated thirteen Crohn's patients with Remicade observed that "[a]dverse events for the 13 patients were usually mild except for 4 patients that suffered from anaphylactic shock, disseminated eruption (2) and eosiniphilic pneumonitis." (Doc. 128-5 at 1).[3]

Dr. Thornton also relied on S. Chatterjee et al., *Severe interstitial pneumonitis associated with infliximab therapy*, Scand. J. Rheumatol. 2004; 33(4):276-277.

This report concerned an eighty-four-year-old patient afflicted with rheumatoid arthritis, not Crohn's disease. After being treated with infliximab, the patient developed "end-stage pulmonary fibrosis." (Doc. 128-8 at 1). The authors of the report, citing "[a] strong temporal association [between] initiation of infliximab and rapid development of interstitial lung disease," stated that "our case . . . suggests the possibility of induction of [interstitial lung disease] by infliximab." (*Id.* at 2).

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[2] Because Dotan's report is in Hebrew, Dr. Thornton read only an English translation of the abstract.

[3] Eosinophilic pneumonitis is characterized by the accumulation of white blood cells in the lungs. None of plaintiff's causation experts diagnosed him with eosinophilic pneumonitis.

However, Chatterjee did not purport to identify a causal relationship between infliximab and interstitial lung disease. Nor did the authors hypothesize a biological mechanism whereby infliximab could have caused the patient's lung injury.

For additional support, Dr. Thornton cited Panagi, et al., *Diffuse Alveolar Hemorrhage After Infliximab Treatment of Crohn's Disease*, Inflamm. Bowel Dis., Vol. 10, No. 3 (May, 2004). This report concerned a Crohn's patient who, "[w]ithin 48 hours after the second infliximab infusion," developed "severe respiratory distress." (Doc. 128-7 at 1). The patient's near-fatal condition included "partially organized intraalveolar hemorrhage," or bleeding into the lungs. Although the authors hypothesized that infliximab was responsible for the patient's injury, they acknowledged that "[t]he exact mechanism by which infliximab may have caused the observed lung results remains unknown." (*Id.* at 4).

According to Dr. Thornton, additional articles in circulation by 2003 described "potential mechanisms of action" by which TNF-α inhibitors like Remicade "might cause unusual direct toxicity through aberrant immune activation." (*Id.* at 2). Dr. Thornton did not identify any reports or studies purporting to test those hypothesized mechanisms. Nor did he conduct his own research on this issue.

To further support his opinion, Thornton looked to the Bradford Hill criteria. These criteria, which were "articulated by world-renowned epidemiologist Sir Arthur Bradford Hill in his seminal methodological article on inferences of causality," *Milward v. Acuity Specialty Prods. Grp., Inc.*, 639 F.3d 11, 17 (1st Cir. 2011), help epidemiologists "mak[e] judgments about whether causation may be inferred from an association." *In re Welding Fume Prods. Liab. Litig.*, 2005 WL 1868046, at *12 (N.D. Ohio 2005).

There are nine Bradford Hill criteria,[4] but Dr. Thornton's report addressed only two: 1) the temporal relationship between infliximab infusions and the onset of symptoms associated with interstitial lung disease; and 2) "challenge/re-challenge," which evaluates whether a patient's condition improves after a given medication is withdrawn or worsens after the same medication is reintroduced. *Rider v. Sandoz Pharms. Corp.*, 295 F.3d 1194, 1199-1200 (11th Cir. 2002).

Thornton opined that temporality criterion was "especially strong," given the body of evidence – i.e., case reports – documenting the onset of "non-infectious, immune-system mediated toxicity" after a second or third dose of infliximab. (Doc. 115-2 at 5).

As for the challenge/re-challenge criterion, Thornton explained that the "ethical restraints of re-exposure of a patient to the same agent once an adverse event has occurred" precluded him from testing whether further Remicade treatment would harm plaintiff. (*Id.*).

At his deposition, Dr. Thornton discussed a third Bradford Hill criterion: coherence, which holds that "[c]oherence between epidemiological and laboratory findings increases the likelihood of an effect." (*Id.*). However, Thornton's testimony on this issue exposed a wide gulf between what the law and epidemiologists understand to be a proper opinion on general causation and Thornton's own opinion.

For example, Thornton testified that he did not attempt to "link" an association between Remicade and an "event," by which he meant an injury or disease. (Doc. 114-2 at 125-126). As he

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[4] Those criteria are: 1) the strength or frequency of the association; 2) the consistency of the association in varied circumstances; 3) the specificity of the association; 4) the temporal relationship between the disease and the posited cause; 5) the dose response curve between them; 6) the biological plausibility of the causal explanation given existing scientific knowledge; 7) the coherence of the explanation with generally known facts about the disease; 8) the experimental data that relates to it; and 9) the existence of analogous causal relationships. *Milward*, *supra*, 639 F.3d at 17.

explained, "this isn't a lab finding thing with regard to what I meant with coherence. It's more coherence from a post-marketing pharmacovigilance mindset of what makes sense within the disease[.]" (*Id.* at 126). He then admitted that his analysis concerned the "regulatory strength" of the association between Remicade and interstitial lung disease, not the "statistical strength" of that association. (*Id.* at 129).

Dr. Thornton also appeared to testify that his causation opinion was directed, not at whether the evidence was sufficient to identify a causal relationship between Remicade and interstitial lung disease, but rather at when Centocor had sufficient data to trigger its duty to warn that Remicade was associated with non-infectious lung disease:

> Q: So am I understanding from your last answer that the way you are looking at the application of these Bradford Hill criteria, it's through your eyeglasses as an [x]FDA person as opposed to if you were a pulmonologist looking at a group of patients?
>
> A: That's correct. At FDA we often grapple with causality, especially in the post-marketing setting, and especially for rare events, and so it's a constant struggle to try to make sense of the noise, and so the Bradford Hill criteria are helpful, very helpful in trying to establish the causality.
>
> Q: And isn't it fair to say that the FDA perspective would be to err on the side of incorporating something in labeling as opposed to saying, it's more likely background noise, let's wait for more information before we make a decision how to treat patient Jones or patient Smith, which a clinician might be thinking of?
>
> A: I can't really speak to that as sort of a given. I think – so I wouldn't say it's a given for an FDA'er.
>
> Q: You think it's the norm or practice?
>
> A: I'd say that's more fair, yeah.

(*Id.* at 130-131; *see also id.* at 77 ("[A]s I read the chronology of the accumulating information about this specific toxicity in Crohn's disease patients, [there was] a critical mass of evidence [that] had

accumulated . . . for Centocor to have taken action . . . to alert FDA of something that needed to change [on the Remicade label])).

Finally, Dr. Thornton stated that his review of plaintiff's medical records revealed "no confounding factors (e.g. no clear infectious etiology or environmental exposure) that may have caused this disease." (Doc. 115-2 at 5).

At the same time, Thornton acknowledged that: 1) plaintiff took Pentasa concurrently with his infliximab treatments; and 2) Pentasa is strongly associated with interstitial lung disease. Nevertheless, Thornton did not try to determine whether Pentasa could have caused plaintiff's lung injury; he relied on another expert's conclusion that Remicade was more likely than Pentasa to have caused plaintiff's injuries.

2. Dr. Tomashefski

Joseph F. Tomashefski is Chairman of the Department of Pathology at the MetroHealth Medical Center in Cleveland and a Professor of Pathology at Case Western Reserve University.

Based on his review of the pertinent records, Dr. Tomashefski opined that plaintiff developed "diffuse lung injury in the form of organizing [diffuse alveolar damage] with increased eosinophils due [to] drug-mediated lung toxicity." (Doc. 116-2 at 9).

Like Dr. Thornton, Dr. Tomashefski concluded that "infliximab-induced severe pulmonary toxicity has become a well recognized complication of [infliximab treatment] and has been reported in patients with rheumatoid arthritis, Crohn's disease, and psoriatic arthritis[.]" (*Id.* at 7).

Dr. Tomashefski's sole basis for that opinion was case reports. He acknowledged that "there are very few reports in the medical literature associating [diffuse alveolar damage] with Remicade." (Doc. 113-1 at 45). Moreover, only one of the three case reports that Tomashefski cited –

Weatherhead, et al., *Interstitial pneumonitis after infliximab therapy for Crohn's disease*, Inflamm. Bowel Dis. 2006; 12:427-428 – involved a patient with Crohn's disease.[5]

Weatherhead's report describes the case of a twenty-two-year-old patient who, after receiving her first infliximab infusion, developed a severe cough that worsened after a second infusion. When her doctors halted the infliximab treatment and began corticosteroid treatment, the patient recovered with no permanent lung damage. The patient was also taking Pentasa concurrently with infliximab, although Pentasa "had been discontinued before the onset of respiratory symptoms[.]" (Doc. 128-9 at 1).

The authors "suspected" that the "primary pathology . . . was a reactive pneumonitis to infliximab[.]" (Doc. 128-9 at 2). But they did not purport to identify – let alone test for – a causal link between infliximab and pulmonary disease.

Although the authors hypothesized a biologic mechanism whereby infliximab, taken in conjunction with methotrexate (a drug commonly used to treat patients with rheumatoid arthritis), could cause certain lung diseases in rheumatoid-arthritis patients (*id.* at 1), the authors did not hypothesize a mechanism whereby taking only infliximab could cause a Crohn's patient to develop interstitial pneumonitis.[6]

Dr. Tomashefski had his own hypothesis as to how Remicade could cause diffuse alveolar damage. He opined that, because drugs of the TNF-α inhibitor class "seem to cause similar types of injury," "it's probably not too far of an assumption to think that Remicade would have similar side

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[5] The other two articles involved patients with rheumatoid or psoriatic arthritis, conditions from which plaintiff does not suffer. (Doc. 116-2 at 10).

[6] The Weatherhead report concludes by noting that, to the authors' knowledge, "there are only 2 other cases of pneumonitis reported with infliximab therapy in Crohn's disease[.]" (*Id.* at 2).

effects as some of the other biological agents." (Doc. 113-1 at 139). But he agreed that his theory was just "speculation." (*Id.*; *see also id.* at 103 (testifying that mechanism is "unknown, and I would just be speculating")).

In opining on specific causation, Tomashefski acknowledged that plaintiff was on two "potentially pneumo-toxic agents, Infliximab and Mesalamine," when he developed respiratory failure. (Doc. 116-2 at 9). He also agreed that neither drug "can be excluded clinically or histologically as a contributing cause of Mr. DeGidio's acute lung injury." (*Id.*).

However, Tomashefski opined that Remicade was the most probable culprit given: 1) the severity of plaintiff's injury; 2) the absence of granulomas (i.e. an inflammation of the lung caused by an infection); and 3) the onset of injury between the second and third infusions of Remicade.

3. Dr. Horowitz

Jeffrey C. Horowitz is an Assistant Professor of Medicine in the Division of Pulmonary and Critical Care Medicine at the University of Michigan Medical School. He was plaintiff's primary treating physician at UMH.

Dr. Horowitz opined that Remicade proximately caused plaintiff's eosinophilic pneumonia, which in turn irreversibly compromised plaintiff's lung functioning. After noting the temporal relationship between plaintiff's Remicade infusions and the onset of his symptoms, Horowitz laid out a causal analysis:

- There was no evidence that plaintiff suffered an infection;
- A lung biopsy revealed a pattern of diffuse alveolar damage with infiltration of eosinophils, lymphocytes, and plasma cells, all of which support an underlying diagnosis of eosinophilic pneumonia;

- Plaintiff was on a stable medication when he started infliximab treatment;

- There was no evidence plaintiff was exposed to a toxic or environmental source of a substance known to cause eosinophilic pneumonia; and
- Eosinophilic pneumonia is a rare condition. Of the known etiologies, idiosyncratic reactions to medication are common, and Remicade "has been reported as a cause of non-infectious interstitial pneumonia."

(Doc. 116-3 at 6).

In opining on general causation, Horowitz acknowledged that the literature discussing patients treated with TNF-α inhibitors who develop non-infectious lung disease was "relatively sparse" and consisted "predominately of case reports, case series or literature reviews." (*Id.* at 5). Dr. Horowitz also testified that, while he had treated "thousands" of patients with lung disease, plaintiff was the only patient who developed diffuse alveolar damage after receiving Remicade. (Doc. 114-1 at 36-37).

Dr. Horowitz acknowledged that more than one hundred drugs have been cited as causes of eosinophilic lung disease. He also noted that "the clinical, radiographic and pathologic features of drug-associated eosinophilic pneumonias are non-specific and overlap with those seen in idiopathic eosinophilic pneumonias" – i.e., those with unknown causes. (Doc. 116-3 at 4).

Given the apparent difficulties in distinguishing between drug-induced and idiopathic eosinophilic diseases, Dr. Horowitz opined that the "diagnosis of drug-induced eosinophilic pneumonia centers on . . . a temporal association between the onset of signs/symptoms and the initiation of the drug." (*Id.*).

Dr. Horowitz was aware that plaintiff was on Pentasa at the time of the injuries, but he did not review the literature on Pentasa and its association with lung injuries. Rather, he was generally familiar with the association between salicylates (the class of drugs to which Pentasa belongs) and idiosyncratic lung toxicity. He rendered no opinions about Pentasa.

Horowitz testified that patients who experience acute, drug-induced interstitial pneumonia generally improve once the drug treatment is withdrawn and steroid treatment begins. He also agreed that plaintiff's condition improved around October 7, 2007, "within days of stopping Pentasa." (Doc. 136-4 at 5).

Discussion

Centocor raises three main arguments in its *Daubert* motions.

It first argues that Dr. Thornton is not qualified to opine on either general or specific causation.[7]

Second, Centocor contends that the experts' general causation opinions are unreliable because each expert: 1) relied solely on case reports to conclude that Remicade can cause interstitial pneumonitis; 2) made unreliable extrapolations from those reports; and 3) failed to describe a biologic mechanism whereby Remicade causes interstitial pneumonitis and diffuse alveolar damage.

Third, Centocor argues that the experts' specific causation opinions are unreliable because no expert could definitely rule out Pentasa or an idiopathic cause as the cause of plaintiff's injury.

Federal Rule of Evidence 702 requires that I perform a "gatekeeping role" before admitting expert testimony. *Daubert*, *supra*, 509 U.S. at 597. The Rule provides that:

> A witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if:
>
> (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;
>
> (b) the testimony is based on sufficient facts or data;

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[7] Centocor further objects to Dr. Thornton's qualifications to opine on the adequacy of the Remicade warning label. Given my disposition of Centocor's other arguments, I do not reach this issue.

(c) the testimony is the product of reliable principles and methods; and

(d) the expert has reliably applied the principles and methods to the facts of the case.

Fed. R. Evid. 702.

My *Daubert* analysis has three components. I first ask whether the witness is qualified to give an opinion on the matter at hand. "When making a preliminary finding regarding an expert's qualifications . . . the court is to examine not the qualifications of a witness in the abstract, but whether those qualifications provide a foundation for a witness to answer a specific question." *MAR Oil Co. v. Korpan*, --- F. Supp. 2d ----, 2013 WL 5406078, at *2 (N.D. Ohio 2013).

Second, I consider whether the expert's testimony is reliable. In *Daubert*, the Court listed several nonexhaustive criteria that help courts identify reliable evidence. They include: 1) whether a theory or technique can be, and has been, tested; 2) whether the technique has been subjected to peer review and publication; and 3) whether the theory or technique enjoys general acceptance within a relevant scientific community. *Daubert*, *supra*, 509 U.S. at 592-594.

"Whether *Daubert*'s specific factors are, or are not, reasonable measures of reliability in a particular case is a matter that the law grants the trial judge broad latitude to determine." *Kumho Tire Co., Ltd. v. Carmichael*, 526 U.S. 137, 153 (1998). In the end, my focus "must be on the principles and methodologies on which the expert's opinion is based, and not on the merits of the expert's conclusions." *MAR Oil*, *supra*, --- F. Supp. 2d at ----, 2013 WL 5406078, at *3.

Third, I consider whether the expert's testimony is relevant to the matter before the court. *Daubert*, *supra*, 509 U.S. at 591-593. The relevance requirement ensures "a fit between the testimony and the issue to be resolved at trial." *MAR Oil*, *supra*, --- F. Supp. 2d at ----, 2013 WL 5406078, at *3.

Plaintiff has the burden of showing, by a preponderance of the evidence, that his experts' testimony is admissible. *Daubert*, *supra*, 509 U.S. at 592.

A. General Causation Opinions

As noted above, each of plaintiff's experts proposes to testify that Remicade can cause interstitial pneumonitis and diffuse alveolar damage.[8]

Centocor raises four issues with this proposed testimony: 1) the experts were unable to cite an epidemiological study identifying an association or causal relationship between Remicade and plaintiff's lung injury; 2) case law establishes that a general causation opinion based entirely on case reports is unreliable; 3) even assuming that case reports could provide a sufficient basis for a general causation opinion, the experts' extrapolations from those reports are unreliable; and 4) no expert could describe, or identify studies describing, the biologic mechanism whereby Remicade causes interstitial pneumonitis and diffuse alveolar damage.

I will address these objections, and plaintiff's responses thereto, in turn.

1. Lack of Epidemiologic Evidence

First, Centocor correctly points out that none of plaintiff's experts identified an epidemiological study finding a cause-and-effect relationship between Remicade and interstitial pneumonitis.

[8] For purposes of this order, I assume, without deciding, that Dr. Thornton is qualified to provide a causation opinion.

Epidemiology is a scientific field concerned with identifying a causal nexus between external factors and disease. *Rider*, *supra*, 295 F.3d at 1198. "Epidemiologic studies are the primary generally accepted methodology for demonstrating a causal relation between the chemical compound and a set of symptoms or a disease." *In re Meridia*, *supra*, 328 F. Supp. 2d at 800.

Although "[n]o requirement exists that a party must offer epidemiologic evidence to establish causation," an expert who "does not rely on th[at] primary methodology for establishing causation [has the burden] to explain his choice of methodologies." *Id.* (emphasis omitted).

Plaintiff counters that his experts did, in fact, rely on "controlled studies" and "epidemiological studies." (Doc. 128 at 20-22). In support, he cites the "Spanish Study," which comprises *Interstitial Lung Disease Induced or Exacerbated by TNF Targeted Therapies: Analysis of 122 case* and *Autoimmune Diseases Induced by TNF Targeted Therapies: Analysis of 233 Cases*. (Docs. 128-13 & 128-15).

However, the Spanish Study is not an epidemiological study, as it does not purport to identify and control for variables or demonstrate a causal relationship between Remicade treatment and interstitial pneumonitis in Crohn's patients.

Rather, the former component of the Spanish Study is a case report describing a single patient who developed interstitial lung disease after taking methotrexate for psoriatic arthritis. (Doc. 128-13 at 2-3).The authors then review other case reports, the vast majority of which (one hundred and eight) involved patients with rheumatoid arthritis. (*Id.* at 4). Moreover, only three case reports focused on patients with inflammatory bowel disease, and even in those cases it is unclear whether those patients had Crohn's disease or ulcerative colitis. (*Id.* at 4-6). Finally, the authors did not

purport to isolate and identify a causal relationship between patients taking only Remicade and interstitial lung disease.[9]

Contrary to plaintiff's representation, the Spanish Study (and the other documents he cites in his opposition papers) are not epidemiological studies. Indeed, plaintiff's experts acknowledged that they relied on case reports, not epidemiological studies.

The absence of epidemiological studies is not fatal to plaintiff's case, but his experts have the burden to explain how their general-causation methodologies remain reliable in the absence of that important evidence. *In re Meridia*, *supra*, 328 F. Supp. 2d at 800.

2. Case Reports

Drs. Thornton, Horowitz, and Tomashefski relied exclusively on case reports to support their opinions that Remicade can cause interstitial pneumonitis and diffuse alveolar damage. That methodology is highly problematic, given the widespread recognition among the federal courts that "case reports alone cannot prove causation." *Id.* at 808.

As a foundation for a causation opinion, case reports have many shortcomings. First, "[c]ase reports make little attempt to screen out alternative causes for a patient's condition." *Glastetter v. Novartis Pharms. Corp.*, 252 F.3d 986, 989-990 (8th Cir. 2001).

Second, case reports "simply describe[ ] reported phenomena without comparison to the rate at which the phenomena occur in the general population or in a defined control group; do not isolate and exclude potentially alternative causes; and do not investigate or explain the mechanism of

[9] The second half of the Spanish Study, which is also limited to a review of case reports, is equally inconclusive. The authors of that paper cited only two Crohn's patients who developed interstitial lung disease. But the paper is silent on whether those patients had taken infliximab. (Doc. 128-15 at 5; *see also id.* at 1 (noting that patients in case reports had received one of three different TNF-α inhibitors)).

causation." *Casey v. Ohio Med. Prods.*, 877 F. Supp. 1380, 1385 (N.D. Cal. 1995); *see also Reference Manual on Scientific Evidence* 475 (Fed. Judicial Ctr. 2000) ("[c]ausal attribution based on case studies must be regarded with caution"). As the Eleventh Circuit aptly noted, "case reports raise questions; they do not answer them." *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1254 (11th Cir. 2005).

Third, case reports "often omit relevant facts about the patient's condition," *Glastetter*, *supra*, 252 F.3d at 989, thereby hampering one's ability to apply any conclusions made in a given report to other cases.

To be sure, some case reports may contain details of the patient's treatment history and even a differential diagnosis, in which a doctor attempts to identify the cause of a patient's condition by ruling out other probable causes. But even those reports "are not reliable enough, by themselves, to demonstrate [a] causal link . . . because they report symptoms observed in a single patient in an uncontrolled context." *Rider*, *supra*, 295 F.3d at 1199. Indeed, even if the report purports to "rule out other potential causes of the effect," it may not "rule out the possibility that the effect manifested in the reported patient's case is simply idiosyncratic or the result of unknown confounding factors." *Id.*

Here, there is no question that plaintiffs' experts based their general-causation opinions solely on case reports. However, no expert tried to explain – let alone persuasively– why those reports provide a reliable basis for concluding that Remicade can cause interstitial pneumonitis. Indeed, as I discuss below, the case reports at issue here suffer from the same flaws identified by the courts in *Rider*, *Glastetter*, and *In re Meridia*.

Because plaintiffs' experts' sole basis for opining that Remicade can cause interstitial pneumonitis is case reports, those experts' methodologies are unreliable under *Daubert*, and their testimony is inadmissible on that basis alone. *See, e.g.*, *Norris v. Baxter Healthcare Corp.*, 397 F.3d 878, 885-886 (10th Cir. 2005) ("Case reports that state that some women with breast implants developed disease do not provide an adequate scientific basis from which to conclude that breast implants in fact cause disease."); *In re Meridia*, 328 F. Supp. 2d at 808.

3. Extrapolations from the Case Reports

In any event, even if case reports, standing alone, could support a reliable general causation opinion, the experts here did not reliably apply the reports to the facts of this case. *See In re Heparin Prods. Liab. Litig.*, 803 F. Supp. 2d 712, 727 (N.D. Ohio 2011) ("[P]laintiffs must still demonstrate that the reasoning or methodology on which their experts base their opinions is scientifically valid and *properly applied to the facts in issue*.") (emphasis added).

For his part, Dr. Thornton merely counted up the available case reports and opined that "the accumulating information about this specific toxicity in Crohn's disease patients" amounted to a "critical mass of evidence" sufficient for "Centocor to have taken action on its own to alert FDA of something that needed to change [on its Remicade warning label]." (Doc. 114-2 at 77).

There are several flaws in that methodology. First, it does not appear that Dr. Thornton accounted for the fact that some of the case reports (the Chatterjee and Ostor reports, for example, *see* Docs. 129-8, 129-11) involved patients with rheumatoid arthritis, not Crohn's disease. He certainly provided no explanation as to why case reports focusing on rheumatoid-arthritis patients provide a reliable jumping-off point for opining on whether Remicade causes interstitial pneumonitis in Crohn's patients.

Second, the Dotan case report, a case report involving a Crohn's patient that Thornton cited, did not purport to identify a causal relationship between Remicade and the patient's interstitial pneumonitis. Nowhere did Thornton explain how this report, which concluded that Remicade is a "relatively safe option [to treat Crohn's disease] after established treatment has failed," support his opinion that Remicade causes interstitial pneumonitis. (Doc. 129-5 at 1)

Finally, it appears that Thornton used case reports to opine primarily on *when* Centocor had sufficient information to trigger a duty to warn of Remicade's association with interstitial lung disease, and not on *whether* there is a meaningful cause-and-effect relationship between Remicade and plaintiff's lung injury. Indeed, Dr. Thornton was rather explicit on this point at his deposition, explaining that he had evaluated the evidence from a "post-marketing pharmacovigilance mindset," and that his analysis concerned "regulatory strength," not "statistical strength." (Doc. 114-2 at 125-126, 129-131).

Dr. Thornton's methodological flaws were not his alone. Like Thornton, Dr. Tomashefski relied on case reports discussing rheumatoid arthritis patients who had been treated with infliximab. But this is problematic, given Tomashefski's (and Thornton's and Horowitz's) acknowledgment that rheumatoid arthritis is strongly associated with interstitial lung disease. It is therefore unclear how the case reports involving rheumatoid-arthritis patients support Tomashefski's opinion that Remicade can cause interstitial lung disease.

To be sure, Tomashefski cited one case report – Weatherhead – in which a Crohn's patient treated with infliximab developed a lung injury. But there are sufficient factual discrepancies between that case and this one to undermine Tomashefski's reliance on it.

To begin, the patient in the Weatherhead report had an acute reaction, whereas plaintiff has a chronic condition. Moreover, while the Weatherhead patient developed a cough after her first infusion of infliximab, plaintiff's symptoms did not manifest until after his second dose of Remicade. This is a significant discrepancy, given the anecdotal evidence that the onset of symptoms usually occurs after a patient's second or third dose of infliximab. Moreover, Weatherhead's patient made a full recovery after corticosteroid treatment, whereas plaintiff experienced permanent lung damage despite such treatment.

Nor am I persuaded that Panagi's case report, *Diffuse alveolar hemorrhage after infliximab treatment of Crohn's disease*, provides a reliable basis for concluding that Remicade can cause interstitial pneumonitis. Indeed, the patient in that case did not develop interstitial pneumonitis or diffuse alveolar damage at all; the patient developed alveolar hemorrhaging, which plaintiff did not experience. (Doc. 128-7 at 4).

Turning to Dr. Horowitz, I note that he, like the other experts, could not identify any case report finding a cause-and-effect relationship between Remicade and interstitial pneumonitis. Moreover, Horowitz testified that plaintiff was the only lung-disease patient out of the "thousands" Horowitz treated who developed diffuse alveolar damage after Remicade infusions. (Doc. 114-1 at 36-37).

Lastly, this is not a case where an overwhelming number of case reports documents a close temporal relationship between Crohn's patients treated with Remicade and interstitial pneumonitis. *Cf. Caraker*, *supra*, 188 F. Supp. 2d at 1035 (suggesting that "an overwhelming amount of case reports of a temporal proximity between a very specific drug and a very specific adverse event might

be enough to make a general causation conclusion sufficiently reliable," but finding that case reports in that case were too few and too diverse to support reliable conclusion).

The Crohn's-specific case reports are few and far between, and the authors of one such report have acknowledged the "isolated" nature of cases where a Crohn's patient experienced interstitial lung disease after taking Remicade. (Doc. 129-8 at 1).

In sum, Drs. Thornton, Tomashefski, and Horowitz did not explain why the case reports, many of which involved patients with RA, provided a reliable basis for concluding that Remicade can cause interstitial pneumonitis. Indeed, it appears from their reports and depositions that plaintiff's experts assumed or took for granted that Remicade can cause interstitial pneumonitis.

Because the experts' extrapolations from the case report are both unsupported and unreliable, their general-causation opinions are inadmissible.

4. Biologic Plausibility

I also find it significant that none of plaintiff's experts could describe the biologic mechanism whereby Remicade could not cause interstitial pneumonitis or diffuse alveolar damage.

"A biologic mechanism is a medically plausible process by which a [drug] can cause a particular injury." *Ryman v. Sec'y of Dep't of Health & Human Servs.*, 65 Fed. Cl. 35, 39 (Fed. Cl. 2005). "The underlying predicates of any cause-and-effect medical testimony are that medical science understands the physiological process by which a particular disease or syndrome develops and knows what factors cause the process to occur." *McClain*, *supra*, 401 F.3d at 1253.

Here, Dr. Tomashefski testified that the mechanism is "unknown," and that he would "just be speculating" if he were to opine on that subject. (Doc. 113-1 at 103). True, he hypothesized that, because Remicade belongs to a class of drugs that "seem to cause similar types of injury," it was not

"too much of an assumption to think that Remicade would have similar side effects as some of th[ose] other biologic agents." (*Id.*). But he admitted that his untested hypothesis was only "speculation." (*Id.*); *cf. Tamraz v. Lincoln Elec. Co.*, 620 F.3d 665, 669 (6th Cir. 2012) (even a "working hypothesis" is not "admissible scientific knowledge").

Furthermore, nowhere in their reports or depositions did Dr. Thornton or Dr. Horowitz opine on the biologic mechanism whereby Remicade causes interstitial lung disease.

Like the doctors themselves, the case reports on which they relied did not identify biologic mechanisms. In the Panagi report, the authors noted that it was unknown how (if at all) Remicade caused the patient's alveolar hemorrhaging. The Chatterjee report was frank in stating that "our knowledge about the potential toxic effects of TNF-inhibitors is quite limited." (Doc. 128-8 at 2-3).

This gap in the evidence would be of particular concern in any case. But it is of even more concern here because at least one of plaintiff's experts was aware that Remicade can *alleviate* non-infectious pulmonary fibrosis in mice. Dr. Thornton acknowledged this "paradox" – that Remicade can allegedly cause and alleviate pulmonary fibrosis – but did not attempt to reconcile it with his opinion. (Doc. 114-2 at 122-124).

Finally, plaintiff argues that, because Remicade "is known to cause allergic reactions [like difficulty breathing, chest pain, and coughing], Remicade has "biological plausibility to cause Plaintiff's non-infectious injury." (Doc. 128 at 45). However, this theory is entirely of plaintiff's devising, and none of his experts has adopted or ratified it.

Conclusion

My task "in assessing evidence proffered under Rule 702 is to determine whether the evidence both rests on a reliable foundation and is relevant to the task at hand." *Best v. Lowe's Home Ctrs., Inc.*, 563 F.3d 171, 176 (6th Cir. 2009).

Given the absence of epidemiological evidence, the experts' exclusive reliance on case reports, their unreliable extrapolations from those reports, and their inability to identify a plausible biologic mechanism whereby Remicade causes interstitial pneumonitis, plaintiff has not shown that the experts' general-causation opinions are admissible. Accordingly, I will grant Centocor's motions to exclude the causation testimony of Drs. Thornton, Tomashefski, and Horowitz.

"The issue of specific causation is material . . . only if plaintiff can demonstrate general causation." *In re Meridia*, *supra*, 328 F. Supp. 2d at 799. Because plaintiff has no admissible evidence to show that Remicade is capable of causing interstitial pneumonitis and diffuse alveolar damage, it follows that plaintiff has no admissible evidence showing that Remicade in fact caused his own lung injuries.

And because plaintiff cannot show the existence of a genuine dispute of material fact in this case without expert testimony, *Terry*, *supra*, 115 Ohio St. 3d at 354-355, I will grant defendant's partial motion for summary judgment.

For the reasons set forth above, it is

ORDERED THAT:

1. Defendant's motion to exclude opinions of Dr. Thornton (Doc. 115) be, and the same hereby is, granted;

2. Defendant's motion to exclude Dr. Tomashefski's and Dr. Horowitz's general and specific causation opinions (Doc. 116) be, and the same hereby is, granted;

3. Defendant's motion for partial summary judgment (Doc.124) be, and the same hereby is granted; and

4. All other outstanding motions be, and the same hereby are, denied as moot.

So ordered

/s/ James G. Carr
Sr. U.S. District Judge